Lung Cancer, Race, and a *CYP*1A1 Genetic Polymorphism

Peter G. Shields, Neil E. Caporaso, Roni T. Falk, Haru Sugimura,[1] Glenwood E. Trivers, B. F. Trump, Robert N. Hoover, Ainsley Weston, and Curtis C. Harris[2]

Laboratory of Human Carcinogenesis, Division of Cancer Etiology [P. G. S., H. S., G. E. T., A. W., C. C. H.], and Biostatistics and Epidemiology Program [N. E. C., R. T. F., R. N. H.], Division of Cancer Etiology, National Cancer Institute, NIH, Bethesda, Maryland 20892, and Department of Pathology [B. F. T.], University of Maryland, Baltimore, Maryland 21201

Abstract

The assessment of human cancer risk using molecular epidemiological techniques involves determining the relative contributions of inherited and acquired genetic predispositions, in the context of environmental exposures. Recently described genetic polymorphisms for *CYP*1A1, a gene involved in the metabolic activation of polycyclic aromatic hydrocarbons, have been associated with lung cancer risk in a Japanese population. We report herein findings from a United States case-control study of lung cancer (56 cases; 48 controls). The polymerase chain reaction followed by an *Msp*1 restriction enzyme digestion was used to analyze constitutive DNA but no association between the restriction fragment length polymorphism and lung cancer risk was found (odds ratio, 0.7; 95% confidence interval, = 0.3–1.6). Analysis of genotype by cumulative smoking status did not reveal an elevated risk among lesser or greater smokers. The presence of the *CYP*1A1 *Msp*1 site-present allele, which was previously found to be associated with Japanese lung cancer risk, was statistically increased in African compared to Caucasian Americans (odds ratio, 2.9; 95% confidence interval, 1.2–2.7). When stratified by race, however, no association between case status and the polymorphism was observed, but the small number of study subjects within each racial group limited the statistical power. Larger studies are required to evaluate the risk of the *CYP*1A1 *Msp*1 polymorphism in African Americans.

Introduction

Human cancer risk assessment using molecular epidemiological techniques is rapidly advancing (1). Determinants of cancer risk such as metabolic activation and detoxification, DNA damage, and DNA repair are partly governed by inheritance whereby wide interindividual variation has been documented (2). PAHs,[3] ubiquitous in the environment, are a class of suspect human carcinogens in which interindividual differences in their metabolic activation have been extensively studied. Laboratory animal studies and mutagenesis assays support a role for PAHs in human carcinogenesis (3, 4) as do epidemiological studies of lung and skin cancer (5). Cytochrome P450 (*CYP*)1A1, the gene that codes for AHH, initiates a multienzyme pathway that activates PAHs to highly electrophilic metabolites, (4, 6) which in turn can activate the *HRAS* protooncogene (7). Human lung and placental AHH activity can vary up to several thousand-fold and is induced by exposure to PAHs, tobacco smoke, dietary factors, and other exposures (8–12). The induction process itself may have a genetic component (13) and AHH-activity is higher in lung cancer cases compared to controls (14–16). These activity assays, however, are technically difficult so that facile genotyping assays, which reflect AHH inducibility or activity, would likely enhance individual cancer risk assessments.

Two closely associated polymorphisms at the *CYP*1A1 gene locus have been identified (17, 18). A RFLP revealed by an *Msp*1 restriction enzyme digestion, located 3′ to the *CYP*1A1 structural gene, was described first (17). The second, located in exon 7 and not an RFLP, is responsible for an isoleucine to valine substitution in the protein catalytic region that affects function (18). Microsomes of yeast cells transfected with the exon 7 mutant or wild-type *CYP*1A1 resulted in different activities upon exposure to benzo [*a*]-pyrene; the former having a higher metabolic activation rate.[4] The absolute quantity of AHH protein, however, was unchanged. In a molecular epidemiological study of Japanese, the presence of the site-present *Msp*1 RFLP was associated with lung cancer (17); the OR was 3 for all cancer patients and 4.6 for squamous cell cancer patients. A limitation of this study was the great difference in lifetime smoking rates and ages in cases *versus* controls. In a follow-up study, the association was later found to be stronger among persons who smoked less (19). In contrast to the Japanese study, Norwegian (20) and Finnish (21) lung cancer case-control studies failed to reveal an association of the *CYP*1A1 genotype with cancer. Whether this reflects a difference in study design or a characteristic of the study population remains to be determined. We present herein results from a United States case-control study designed to explore genetic risk factors for lung cancer.

Methods

Genotyping for *CYP*1A1. Southern blot analysis was performed by enzymatically digesting DNA (5 μg) with *Msp*1

Received 1/5/93; revised 5/6/93; accepted 5/6/93.

[1] Present address: First Department of Pathology, Hamamatsu University, School of Medicine, Hamamatsu, Shizuoka, Japan 431–31.

[2] To whom requests for reprints should be addressed.

[3] Abbreviations used are: PAHs, polycyclic aromatic hydrocarbons; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; CYP, cytochrome P450; OR, odds ratio; AHH, aryl hydrocarbon hydroxylase; CI, confidence interval; SDS, sodium dodecyl sulfate; SSC, standard saline-citrate.

[4] K. Kawajiri, personal communication, 1992.

PM3003565723

Source: https://www.industrydocuments.ucsf.edu/docs/hhnj0001

according to the manufacturer's instructions (Pharmacia, Piscataway, NJ). The DNA was then subjected to agarose gel (0.8%) electrophoresis. The gels were treated with NaOH (400 mM) and NaCl (0.6 M) and neutralized with NaCl (1.5 M) and Tris-HCl (500 mM; pH 8.0). The DNA was immobilized on nylon membranes (Bio-Trace-Gelman; Ann Arbor, MI) under vacuum and hybridized with a *CYP*1A1 complementary DNA probe (kindly provided by Dr. F. Gonzalez) under stringent conditions (1% dextran sulfate, 1 M NaCl, 1% SDS at 65°C for 16 h). The membranes were washed with 2 × SSC twice (room temperature; 15 min), 2 × SSC with 1% SDS twice (65°C; 25 min), and then 0.1 × SSC with 1% SDS (room temperature; 10 min). X-ray films (Eastman Kodak, Rochester, NY) were exposed to the membranes for the detection of restriction fragments, the sizes of which were determined by comparison with λ DNA enzymatically digested with *Bst*EII.

PCR amplification (0.5 μg) was performed using primer C44 (5'-TAGGAGTCTTGTCTCATGCCT-3') located at 447–458 bases and primer C47 (5'-CAGTGAAGAGGTGTAGCCGCT-3') at 129–150 bases or primer 1 (5'-AGTCTGTTTGAGGGACAAGA-3') located at 160–180 bases downstream from the polyadenylation signal (18). Primer pair C47/C44 was used in most cases except when product could not be obtained. In those cases, primer pair 1/C44 was successful (n = 23). There was complete concordance in genotyping for the two primer pairs. Reactions were carried out in Tris-HCl (10 mM; pH 8.3), KCl (50 mM), $MgCl_2$ (3 mM), deoxyribonucleotide-triphosphates (1.875 μM; Pharmacia), primer (12.5 μM each), and Taq polymerase (5 units; Perkin Elmer, Norwalk, CO). Amplification occurred (DNA Thermal Cycler; Perkin Elmer) by denaturing at 94°C for 4 min, followed by 35 cycles of 94°C for 60 s, 52°C for 60 s and 72°C for 60 s, and a final extension step of 72°C for 4 min. PCR amplification product (339 base pairs for primer pair C47/C44 and 308 base pairs for primer pair 1/C44; 80 μl) was filter purified (Centricon 100; Amicon, Beverly, MA) and an aliquot (21 μl) was subjected to an *Msp*1 restriction enzyme digestion (30 units) in buffer (10 mM Tris-HCl, pH 7.5–10 mM; $MgCl_2$-KCl 10 mM), β-mercaptoethanol (1 mM), and bovine serum albumin (0.1 mg/ml) at 37°C for 2 h. Additional *Msp*1 enzyme was added (15 units) and the sample was incubated for an additional 2 h. Samples were then analyzed by agarose gel (2.2%) electrophoresis. The wild type allele is resistant to the *Msp*1 restriction enzymes, yielding either a 339-base pair fragment for primer pairs C47/C44 or a 308-base pair fragment for primer pair 1/C44. Alleles sensitive to the *Msp*1 in restriction enzyme is identified by 134- and 205- or 103- and 205-base pair fragments, respectively.

To validate the PCR genotyping method, Southern blot analysis was used as a correlative method in a subset of individuals. DNA samples were obtained from a Baltimore, MD, autopsy donor program and also from octogenarian Japanese (n = 95). All samples were analyzed by Southern blot and samples representing all these possible genotypes were chosen. These samples were then analyzed by PCR and *Msp*1 restriction digestion. For the case-control study, the PCR method was subsequently used to analyze WBC DNA.

Subjects. A case-control study of lung cancer was conducted between 1985 and 1989, as previously described (22). A total of 188 subjects were enrolled, of whom 104 had DNA suitable for genotyping. This subset was similar with regards to age, gender, race, and smoking history as the larger sample. The cases had newly diagnosed and pathologically documented primary lung cancer identified at participating hospitals in Baltimore, MD. Two hospital-based control groups were selected. The first group (n = 31) consisted of outpatients with chronic obstructive pulmonary disease, defined by the presence of abnormal pulmonary function (Forced Expiratory Volume 1% ≤ 75) or with asthma and a history of greater than 40 pack-years of tobacco smoking (number of packs/day × the number of consumption years). The second control group (n = 15) was patients with cancer at anatomical sites other than lung or bladder. All study subjects completed an extensive questionnaire administered by a trained interviewer, covering medical, residential, occupational, and smoking history.

Statistical Analysis. OR estimates of the relative risk with 95% confidence intervals were used to describe the relation of lung cancer to *CYP*1A1 genotype (23, 24) Logistic regression models were used to adjust for age, race, gender, and other variables when sufficient numbers were available (25, 26). Crude ORs were virtually unchanged by adjustment for these factors; therefore, unless indicated, only crude ORs are presented. Gene frequencies and tests for Hardy-Weinberg equilibrium were calculated (27).

Results

In order to validate the assay, Southern analysis was performed on DNA samples from Japanese and United States individuals unrelated to the case-control study (n = 95). Electrophoretic analysis revealed two fragments hybridizing to the *CYP*1A1 probe at 1.9 and 2.3 kilobases as previously reported (17) (Fig. 1*A*). A subset of individuals (n = 24; 2 homozygote site absent, 5 heterozygotes and 17 homozygote site present) were then chosen for analysis by PCR and RFLP. There was 100% concordance between the PCR and Southern blot methods. In the 95 subjects, the allelic frequency for the *Msp*1 site present allele was found to be 10% in Americans and 29% in octogenerian Japanese.

DNA samples from 104 case-control study subjects were amplified and subjected to *Msp*1 restriction enzyme digestion (Fig. 1*B*).

The characteristics of these individuals are listed in Table 1. The cases were sightly older than controls. Control subjects tended to have greater smoking histories, reflecting the study design favoring smokers by selecting persons with chronic obstructive pulmonary disease. Among the controls, the allelic frequency for the *CYP*1A1 polymorphism met Hardy-Weinberg equilibrium with African and Caucasian Americans evaluated separately. The allelic frequency for the site present allele in African and Caucasian American controls was 24 and 14%, respectively.

This study did not reveal a difference in genotype frequency between cases and controls (Table 2). Overall, the ORs were 0.7 (95% CI, 0.3–1.8) and 0.5 (95% CI, = 0.1–3.2) for the heterozygote (W/M) and the homozygous site-present genotype (M/M), respectively. Only 5 subjects (2 cases and 3 controls) were M/M; these subjects were combined with the W/M individuals in subsequent analyses, which yielded an OR of 0.7 (95% CI, 0.3–1.6). When analyzed by histology, no individual subtype was found to be associated with the polymorphism (Table 3). Specifically, there was no increase in homozygous restriction site-present or heterozygote individuals with squamous cell cancer. Risks for the *CYP*1A1 genotype according to lifetime tobacco consumption were estimated (Table 4), but the lack of association with lung cancer persisted.

PM3003565724

Source: https://www.industrydocuments.ucsf.edu/docs/hhnj0001

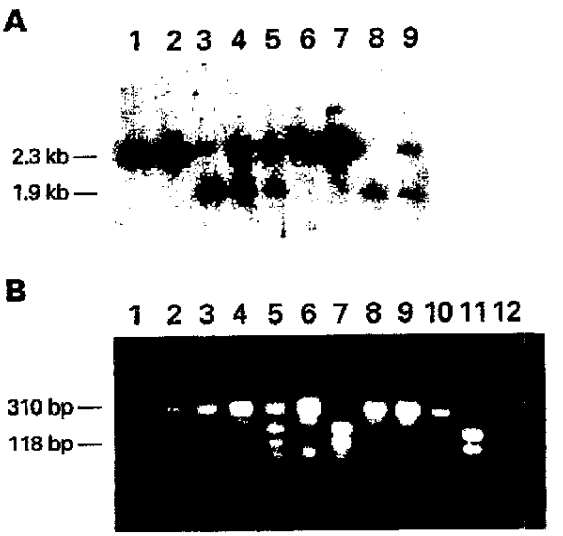

Fig. 1. *A*, Southern blot analysis for *CYP*1A1 genotyping. A 2.3-kilobase band indicates the wild-type allele while the 1.9-kilobase band indicates the mutant allele. Genotypes are homozygous site-absent (*Lanes 1, 2, 6,* and *7*), heterozygotes (*Lanes 4, 5,* and *9*), and homozygous site-present (*Lanes 3* and *8*). DNA is amplified by the polymerase chain reaction and then subjected to *Msp*1 restriction enzyme digestion for *CYP*1A1 locus (*B*) yielding either a 308-base pair fragment or 103-and 205-base pair fragments. The genotyping possibilities, therefore, are homozygous site-absent (*Lanes 3, 4, 6, 8-10*), heterozygotes (*Lanes 1, 2,* and *5*) and homozygous site-present (*Lanes 7* and *11*). PCR is performed without DNA to assess for contamination (*Lane 12*). *bp*, base pairs.

Table 1 Distribution of cases and controls according to demographic characteristics

Demographics	Race		
	African American	Caucasian	Total
n^a	51	53	104
Age (mean)			
Cases	64	66	65
Controls	60	63	62
Gender (male/female)			
Cases	27/1	27/1	54/2
Controls	20/3	25/0	45/3
Pack-years (mean)[b]			
Cases	55	52	55
Controls	47	73	61

[a] Number of subjects with available DNA.
[b] Pack-years = average number of packs smoked/day × total number of years spent smoking.

A difference in the genotype frequency between African and Caucasian Americans (combining cases and controls) was evident (Table 5). The former was more likely to be either a heterozygote or homozygous site-present genotype (OR, 2.9; 95% CI, 1.2–7.1). Analysis of cancer risk by *CYP*1A1 genotype within each racial group still failed to reveal an association (Table 5).

Table 2 Distribution of *CYP*1A1 genotypes in lung cancer cases and controls

Case status	W/W[a]	W/M	M/M
Cases (n = 56)	43	11	2
Controls (n = 48)	33	12	3
OR (by genotype)[b]	1.0	0.7 (0.3–1.8)	0.5 (0.1–3.2)
OR (combined genotype)	1.0	0.7 (0.3–1.6)	

[a] W/W, homozygous site-absent; W/M, heterozygote; M/M, homozygous site-present.
[b] Numbers in parentheses, 95% confidence intervals. Trend test for overall OR, P = 0.675.

Table 3 Distribution of *CYP*1A1 genotypes by lung cancer histology

Histology	W/W[a]	W/M or M/M	OR[b]
Adenocarcinoma	14	4	0.6 (0.2, 2.2)
Squamous cell	20	9	1.0 (0.4, 2.7)
Large cell	4	0	-
Small cell	5	0	-
Pooled controls	33	15	1.0

[a] W/W, homozygous site-absent; W/M, heterozygote; M/M, homozygous site-present.
[b] Numbers in parentheses, 95% confidence intervals.

Earlier analyses showed a statistically significant excess of extensive metabolizers of debrisoquine among our lung cancer cases. Although not genetically linked, the *CYP2D6* metabolic phenotype was examined in relation to *CYP*1A1 genotype, but no association was observed. Separately, the risk associated with the *CYP*1A1 genotype remained relatively unchanged after adjustment for age, race, tobacco use, gender, and debrisoquine phenotype (OR, 0.76; 95% CI, 0.3–2.2 for at least one site-present allele).

Discussion

The results from this lung-cancer case-control of United States individuals do not show a relationship between the *CYP*1A1 *Msp*1 polymorphism and lung cancer risk, even when examined by histological subtype or cigarette consumption. We did find an excess frequency of the homozygote site-present allele in African Americans. However, analysis within race still failed to reveal a relationship to lung cancer, perhaps due to the small number of study subjects and thus a limitation in statistical power. These results were consistent with studies of European groups (20, 21) but contrast with those in Japanese (17, 19). In our study, as in the European studies (20, 21), homozygous site-present alleles were relatively uncommon, with a gene frequency of 14% among Caucasian controls. Among the Japanese, and among our African American controls, this variant allele was more common (17); in these populations the gene frequency was 33% (19) and 24% (this study), respectively. Several factors may explain the contrasting results of cancer risk for the *CYP*1A1 polymorphism: (a) the lower frequency of mutant alleles in European and American populations may limit the statistical power of these studies; (b) our selection of controls with a history of relatively long-term and heavy smoking minimizes the possibility of finding an effect in persons exposed to little or no tobacco smoke (19); (c) the *Msp*1 RFLP may not be associated with the exon 7 mutation in the American study group, although this was not found in Europeans (21) (this hypothesis is currently being tested in Af-

PM3003565725

Source: https://www.industrydocuments.ucsf.edu/docs/hhnj0001

Table 4 Odds ratios for *CYP*1A1 mutant allele, according to lifetime cigarette consumption[a]

Case status	Pack-years[b]					
	<40		40–59		>60	
	W/W	W/M or M/M	W/W[c]	W/M or M/M	W/W	W/M or M/M
Case	16	5	13	5	13	3
Control	9	4	8	2	15	8
OR[d]	1.0	0.7 (0.2–3.3)	1.0	1.5 (0.2–9.9)	1.0	0.4 (0.1–2.0)

[a] Excludes 1 case and 2 controls with incomplete smoking history.
[b] Pack-years = average number of packs smoked/day × total number of years spent smoking.
[c] W/W, homozygous site-absent; W/M, homozygote; M/M, homozygous site-present.
[d] Numbers in parentheses, 95% confidence intervals.

Table 5 Distribution of *CYP*1A1 genotype according to race and case status

Case status	W/W[a]	W/M	M/M
African Americans	32	16	3
Cases (n = 28)	18	9	1
Controls (n = 23)	14	7	2
ORs	1.0		0.9 (0.3–2.7)[b]
Caucasian Americans	44	7	2
Cases (n = 28)	25	2	1
Controls (n = 25)	19	5	1
ORs	1.0		0.4 (0.9–1.6)

[a] W/W, homozygous site-absent; W/M, heterozygote; M/M, homozygous site-present.
[b] Numbers in parentheses, 95% confidence intervals.

rican Americans); and (d) the *CYP*1A1 genetic polymorphism may be a risk factor for lung cancer and chronic obstructive lung disease so the genotype frequency may be equally elevated in these groups compared to the general population, but not different from each other.

The increased frequency of the *CYP*1A1 *Msp*1 site-present allele in African Americans is consistent with epidemiological data for cancer risk in this race *versus* that of Caucasians. Furthermore, earlier findings from this study population showed racial differences among several genetic polymorphisms, including debrisoquine metabolism (28), *CYP2D6-B* mutations,[5] *CYP2E1* (29), *HRAS-1* rare alleles (30), *L-myc* (31), and *p53* (32). This underscores the need to analyze racial groups separately when evaluating genetic polymorphisms and cancer risk.

A relationship between the *CYP*1A1 and *CYP2D6* polymorphisms was explored because the extensive metabolizer phenotype of debrisoquine has been associated with an increased risk of lung cancer, especially among persons who smoke cigarettes or are exposed to polycyclic aromatic hydrocarbons (22, 33). In addition, a mechanistic relationship to the metabolism of carcinogens has not been adequately demonstrated and the frequency of *CYP2D6-B* mutations differ significantly between African and Caucasian Americans.[5] Thus, we hypothesized that the *CYP2D6* mutation(s) might interact with *CYP*1A1 mutations for lung cancer risk. No such association was found.

In conclusion, the previously identified *CYP*1A1 *Msp*1 RFLP was not associated with lung cancer risk in this American case-control study, even within racial or histological groups. However, the small sample size may have limited our ability to detect an effect, particularly among African Americans, so that further study is warranted. It also remains to be established whether the *CYP*1A1 *Msp*1 RFLP is associated with the exon 7 mutation in African Americans.

[5] Unpublished observations.

Acknowledgments

The authors wish to thank Dorothea Dudek for her editorial assistance.

References

1. Shields, P. G., and Harris, C. C. Molecular epidemiology and the genetics of environmental cancer. JAMA, *266:* 681–687, 1991.

2. Harris, C. C. Interindividual variation among humans in carcinogen metabolism, DNA adduct formation and DNA repair. Carcinogenesis (Lond.), *10:* 1563–1566, 1989.

3. Nebert, D. W. The *Ah* locus: genetic differences in toxicity, cancer, mutation, and birth defects. Toxicology, *20:* 153–174, 1989.

4. Phillips, D. H. Fifty years of benzo(a)pyrene. Nature (Lond.), *303:* 468–472, 1983.

5. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Vol. 1–42. Lyon, France: International Agency for Research on Cancer, 1987.

6. Osborne, M. R., and Crosby, N. T. Benzopyrenes. *In:* Cambridge Monographs on Cancer Research, p. 73–164. New York: Cambridge University Press, 1987.

7. Marshall, C. J., Vousden, K. H., and Phillips, D. H. Activation of c-*Ha-ras*-1 proto-oncogene by *in vitro* modification with a chemical carcinogen, benzo(*a*)pyrene diol-epoxide. Nature (Lond.), *310:* 586–589, 1984.

8. Sabadie, N., Richter-Reichhelm, H. B., Saracci, R., Mohr, U., and Bartsch, H. Inter-individual differences in oxidative benzo(a)pyrene metabolism by normal and tumorous surgical lung specimens from 105 lung cancer patients. Int. J. Cancer, *27:* 417–425, 1981.

9. Trell, L., Korsgaard, R., Janzon, L., and Trell, E. Distribution and reproducibility of aryl hydrocarbon hydroxylase inducibility in a prospective population study of middle-aged male smokers and nonsmokers. Cancer (Phila.), *56:* 1988–1994, 1985.

10. Conney, A. H. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic aromatic hydrocarbons: G. H. A Clowes Memorial Lecture. Cancer Res., *42:* 4875–4917, 1982.

11. Fujino, T., Gottlieb, K., Manchester, D. K., *et al.* Monoclonal antibody phenotyping of interindividual differences in cytochrome P-450-dependent reactions of single and twin human placenta. Cancer Res., *44:* 3916–3923, 1984.

12. Manchester, D. K., and Jacoby, E. H. Sensitivity of human placental monooxygenase activity to maternal smoking. Clin. Pharmacol. Ther., *30:* 687–692, 1981.

13. Nowak, D., Schmidt-Preuss, U., Jorres, R., Liebke, F., and Rudiger, H. W. Formation of DNA adducts and water-soluble metabolites of benzo[a]pyrene in human monocytes is genetically controlled. Int. J. Cancer, *41:* 169–173, 1988.

14. Kouri, R. E., McKinney, C. E., Slomiany, D. J., Snodgrass, D. R., Wray, N. P., and McLemore, T. L. Positive correlation between high aryl hydrocarbon hydroxylase activity and primary lung cancer as analyzed in cryopreserved lymphocytes. Cancer Res., *42:* 5030–5037, 1982.

PM3003565726

Source: https://www.industrydocuments.ucsf.edu/docs/hhnj0001

15. Hawke, L. J., and Farrell, G. C. Increased binding of benxo[a]pyrene metabolites to lymphocytes from patients with lung cancer. Cancer Lett., *30:* 289–297, 1986.

16. Rudiger, H. W., Nowak, D., Hartmann, K., and Gerutti, P. A. Enhanced formation of benzo(a)pyrene: DNA adducts in monocytes of patients with a presumed predisposition to lung cancer. Cancer Res., *45:* 5890–5894, 1985.

17. Kawajiri, K., Nakachi, K., Imai, K., Yoshii, A., Shinoda, N., and Watanabe, J. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome *P450IA1* gene. FEBS Lett., *263:* 131–133, 1990.

18. Hayashi, S., Watanabe, J., Nakachi, K., and Kawajiri, K. Genetic linkage of lung cancer-associated *MspI* polymorphisms with amino acid replacement in the heme binding region of the human cytochrome *P450IA1* gene. J. Biochem. (Tokyo), *110:* 407–411, 1991.

19. Nakachi, K., Imai, K., Hayashi, S., Watanabe, J., and Kawajiri, K. Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. Cancer Res., *51:* 5177–5180, 1991.

20. Tefre, T., Ryberg, D., Haugen, A., *et al.* Human *CYP1A1* (cytochrome P1450) gene: lack of association between the *Msp*I restriction fragment length polymorphism and incidence of lung cancer in a Norwegian population. Pharmacogenetics, *1:* 20–25, 1991.

21. Hirvonen, A., Husgafvel-Pursiainen, K., Karjalainen, A., Anttila, S., and Vainio, H. Point-mutational *Msp*I and Ile-Val polymorphisms closely linked in the *CYP1A1* gene: lack of association with susceptibility to lung cancer in a Finnish study population. Cancer Epidemiol., Biomarkers & Prev., *1:* 485–489, 1992.

22. Caporaso, N. E., Tucker, M. A., Hoover, R., *et al.* Lung cancer and the debrisoquine metabolic phenotype. J. Natl. Cancer Inst., *85:* 1264–1272, 1990.

23. Mantel, N., and Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst., *22:* 719–748, 1959.

24. Woolf, A. On estimating the relation between blood group and disease. Ann. Hum. Genet., *19:* 251–254, 1954.

25. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research, Vol. 1. The Analysis of Case-Control Studies. Lyon, France: International Agency for Research on Cancer, 1980.

26. Prentice, R. Use of the logistic model in retrospective studies. Biometrics, *32:* 599–606, 1979.

27. Principle of Population Genetics, Ed. 2, pp. 31–40. Sunderland, MA: Sinauer Association, 1989.

28. Relling, M. V., Cherrie, J., Schell, M. J., Petros, W. P., Meyer, W. H., and Evans, W. E. Lower prevalence of the debrisoquin oxidative poor metabolizer phenotype in American black *versus* white subjects. Clin. Pharmacol. Ther., *50:* 308–313, 1991.

29. Kato, S., Shields, P. G., Caporaso, N. E., *et al.* Cytochrome P450IIE1 genetic polymorphisms, racial variation, and lung cancer risk. Cancer Res., *52:* 6712–6715, 1992.

30. Sugimura, H., Caporaso, N. E., Hoover, R. N., *et al.* Association of rare alleles of the Harvey *ras* protooncogene locus with lung cancer. Cancer Res., *50:* 1857–1862, 1990.

31. Tamai, S., Sugimura, H., Caporaso, N. E., et al. Restriction fragment length polymorphism analysis of the *c-myc* gene locus in a case-control study of lung cancer. Int. J. Cancer, *46:* 411–415, 1990.

32. Weston, A., Perrin, L. S., Forrester, K., *et al.* Allelic frequency of a p53 polymorphism in human lung cancer. Cancer Epidemiol., Biomarkers & Prev., *1:* 481–483, 1992.

33. Ayesh, R., Idle, J. R., Ritchie, J. C., Crothers, M. J., and Hetzel, M. R. Metabolic oxidation phenotypes as markers for susceptibility to lung cancer. Nature (Lond.), *312:* 169–170, 1984.

PM3003565727

Source: https://www.industrydocuments.ucsf.edu/docs/hhnj0001